REMARKS

In response to the Office Action of August 26, 2004, Applicants have amended the specification and claims, which, when considered with the following remarks, is deemed to place the present application in condition for allowance. Favorable consideration of all pending claims is respectfully requested.

The Examiner has objected to the disclosure due to a number of informalities, such as the status of the parent application 10/234,273 not updated in the preliminary amendment filed previously. Other grammatical and spelling errors also form the basis for the objection. By this amendment, the status of parent application serial number 10/234,273 has been updated as abandoned. Also by this amendment, grammatical and spelling errors in the specification have been corrected. Withdrawal of the objection to the disclosure due to the various informalities outlined by the Examiner is therefore respectfully requested.

Claims 10-13, 15, 16, 17, 21, 23, 25, 26, and 30 have been rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Examiner objects to the "preferably clauses" recited in claims 10-13, 15, and 16. As suggested by the Examiner, the "preferably clauses" have been deleted from the claims and have now been made the subject matter of dependent claims. Other clauses to which the Examiner has objected, i.e., "in particular", "such as", and "for example" have also been canceled from the claims and recited in dependent claims. Claims 21, 23, and 30 are allegedly indefinite because these claims refer to a component (d) but the claims on which claims 21, 23, and 30 depend do not recite a component (d). As presently amended, claims 21 and 22 depend from claim 18, which claim recites a component (d). Claim 30 has been amended to recite component (e')

rather than component (d). Withdrawal of the rejection of claims 10-13, 15, 16, 17, 21, 23, 25, 26, and 30 under 35 U.S.C. §112, second paragraph, is therefore warranted.

Claims 2-7, 9, 10, 18, 20, 22, and 23 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-7 of U.S. Patent No. 6,468,968. Applicants respectfully traverse the rejection and respectfully submit that the claims of the pending application are patentably distinct from claims 1-7 of U.S. Patent No. 6,468,968.

Applicants' traversal is predicated on the following remarks. Claims 1-7 of the '968 patent are directed to a pharmaceutical composition for oral administration comprising a cyclosporin other than cyclosporin A in a carrier medium comprising sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid, wherein the fatty acid is obtained from vegetable oil. As presently amended, claims 2-7, 10, 18, 20 and 22 recite or depend from a claim which recites "[a] pharmaceutical composition comprising a) a cyclosporin as active ingredient in a carrier medium consisting essentially of b+c) a transesterification product of a hydrogenated vegetable oil with glycerol or propylene glycol." Claims 1-7 of the '968 patent, directed to sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid wherein the fatty acid is obtained from vegetable oil, neither anticipate nor suggest presently amended claims 2-7, 10, 18, 20 or 22. Withdrawal of the obviousness-type double patenting rejection is therefore warranted.

Claims 2-7, 9, 10, 18, 20, 22, and 23 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-7 of U.S. Patent No. 6,306,825. Applicants respectfully traverse the rejection and respectfully submit that presently pending claims 2-7, 9, 10, 18, 20, and 22 are patentably distinct from claims 1-7 of the '825 patent for the following reasons. Claims 1-6 of the '825 patent are directed to a pharmaceutical composition for oral administration comprising cyclosporin a as active ingredient in a carrier medium

comprising sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid, wherein the fatty acid is obtained from vegetable oil." Claim 7 of the '825 patent recites "a pharmaceutical composition for oral administration comprising cyclosporin a as active ingredient in a carrier medium comprising a reaction product of a natural or hydrogenated castor oil and ethylene oxide; and sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid, wherein the fatty acid is obtained from vegetable oil."

As presently amended, claims 2-7, 10, 18, 20 and 22 recite or depend from a claim which recites "[a] pharmaceutical composition comprising a) a cyclosporin as active ingredient in a carrier medium consisting essentially of: b+c) a transesterification product of a hydrogenated vegetable oil with glycerol or propylene glycol." Claims 1-6 of the '825 patent, directed to a pharmaceutical composition for oral administration comprising cyclosporin a as active ingredient in a carrier medium comprising sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid, wherein the fatty acid is obtained from vegetable oil, do not anticipate nor suggest the presently amended claims 2-7, 10, 18, 20 or 22. Similarly, claim 7 of the '825 patent, directed to a pharmaceutical composition for oral administration comprising cyclosporin a as active ingredient in a carrier medium comprising a reaction product of a natural or hydrogenated castor oil and ethylene oxide; and sorbitol mono-, di-, tri-, and tetra-esters of a fatty acid, wherein the fatty acid is obtained from vegetable oil, does not anticipate or suggest the presently claimed invention as recited in claims 2-7, 9, 10, 18, 20, 22, or 23. Withdrawal of the obviousness-type double patenting rejection is therefore warranted.

Claims 1-8, 10, 12, 17, 18, 20, 22, and 23 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-12 of U.S. Patent No. 6,262,022. Applicants respectfully submit that the rejection of claims 1-8, 10, 12, 17, 18, 20, and 23 over claims 1-12 of U.S. Patent No.

6,262,022 will be resolved by an appropriate terminal disclaimer upon the allowance of claims under consideration.

Claim 1 has been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-64 of U.S. Patent No. 5,916,589. Applicants respectfully traverse the rejection for the following reasons. As presently amended, claim 1 recites "a pharmaceutical composition for oral administration comprising: a) a cyclosporin as active ingredient in a carrier medium consisting essentially of b) a fatty acid triglyceride and c) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester." Claims 1-48 of the '589 patent recite a hydrophilic component other than a polyoxyethylene glycolated natural or hydrogenated vegetable oil and other than water, a triglyceride lipophilic component and a polyoxyethylene glycolated natural or hydrogenated vegetable oil surfactant. (claims 1-48). Claims 49-64 are directed to methods of reducing the influence of bile acids and salts on the bioavailability of cyclosporin A in a patient's gastrointestinal system during cyclosporin A therapy. There is no suggestion in any of claims 1-64 of the '589 patent for a pharmaceutical composition comprising cyclosporin as active ingredient in a carrier medium consisting essentially of a fatty acid triglyceride and a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester. The subject matter of presently amended claim 1 is therefore patentably distinct from claims 1-64 of the '589 patent. Withdrawal of the rejection of claim 1 under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-64 of U.S. Patent No. 5,916,589 is therefore warranted.

Claim 2 has been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-13 of U.S. Patent No. 5,652,212. Applicants respectfully submit that the rejection of claim 2 over U.S. Patent

No. 5,652,212 will be resolved by an appropriate terminal disclaimer upon the allowance of claims under consideration.

Claims 1-20, 22, 23, and 27-37 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly unpatentable over claims 1-22 of U.S. Patent No. 5,639,724. Applicants respectfully submit that the rejection of claims 1-20, 22, 23 and 27-37 over U.S. Patent No. 5,639,724 will be resolved by an appropriate terminal disclaimer upon the allowance of claims under consideration.

Claim 1 has been rejected under 35 U.S.C.§ 102(e) as allegedly anticipated by U.S. Patent No. 5,916,589. The '589 patent has been cited for disclosing in Examples 1.6-1.8 cyclosporin-containing compositions comprising Miglyol 812 (which comprises fatty acid triglycerides) and glycerol monooleate (which is a glycerol fatty acid partial ester). Applicants respectfully traverse the rejection of claim1 for the following reasons. Examples 1.6-1.8 of the '589 patent disclose compositions comprising various quantities (mg/capsule) of cyclosporin, 1, 2-Propyleneglycol, Miglyol 812, Cremophor RH40, and Glycerol monooleate. As presently amended, claim 1 recites "a pharmaceutical composition for oral administration comprising: a) a cyclosporin as active ingredient in a carrier medium consisting essentially of b) a fatty acid triglyceride and c) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester." Claim 1 does not recite Cremophor RH 40,which is a reaction product of a natural or hydrogenated castor oil and ethylene oxide. Claim 1 also does not recite both propylene glycol and a glycerol fatty acid partial ester. Claim 1 is therefore distinguished from the teaching of the '589 patent and withdrawal of the rejection of claim 1 under 35 U.S.C.§ 102(e) is respectfully requested.

Claim 1 has also been rejected as allegedly anticipated under 35 U.S.C. § 102(b) by Cavanak U.S. Patent No. 4,388,307. Cavanak is cited for teaching cyclosporin-containing compositions comprising saturated fatty acid triglycerides and

mono- or di-glycerides of fatty acids. Applicants respectfully traverse the rejection of claim 1 for the following reasons. The '307 patent teaches oral dosage forms of cyclosporin comprising co-solvents, ethanol and vegetable oils such as olive oil and corn oil. For instance, Example 1 of the '307 patent teaches a drink solution comprising 10 parts by weight of Labrafil, ca. 3 parts by weight of cyclosporin A, 3 parts by weight of ethanol and 5 parts by weight of olive oil or corn oil. Example 6 of the '307 patent discloses capsules for oral administration. 200 mg of cyclosporin A are dissolved on stirring in a mixture of 600 mg Glycerol mono-oleate and 30 mg ethanol at 30° C. As described on page 10 of the present specification, the carrier systems of the present invention are oil-based compositions, which are not aqueous emulsions and which do not require the presence of additional solvents, co-solvents or solubilizers, for example ethanol or Labrafils or the like. As presently amended, claim 1 recites "a pharmaceutical composition for oral administration comprising: a) a cyclosporin as active ingredient in a carrier medium consisting essentially of b) a fatty acid triglyceride and c) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester." Claim 1 is therefore distinguished from the teaching of Cavanak U.S. Patent No. 4,388,307. Withdrawal of the rejection of claim 1 under 35 U.S.C. §102(b) is therefore warranted.

Claims 1-8, 10-14, 17-24, 26-30 and 32-37 have been rejected under 35 U.S.C.§ 102(b) as allegedly anticipated by Belgian Patent No. 895 724 in view of Applicants' admission of the prior art at page 9, lines 26-30; page 15, lines 17-32; and page 19, lines 16-18 and 21-22, of the specification. The Examiner has asserted that the Belgian Patent '724 teaches cyclosporin compositions comprising Dihydrocyclosporin D and a carrier medium comprising ethanol, "MAISINE®", and optionally "CREMOPHOR® RH 40" or "IMWITOR® 742" or "LABRAFIL® 2125".

Applicants respectfully traverse the rejection for the following reasons. Belgian Patent No. 895,724 describes two oral formulations of cyclosporin. The first formulation comprises 5-10% [Dihydro-MeBmt]^1-[Val]^2-Ciclosporin, 10-12% ethanol, 30-40% MAISINE, ca. 4% CREMOOPHORE and 51-30% Labrafil (i.e., to 100%). As stated in the Belgian patent, CREMOPHORE RM 40 is the reaction product of castor oil hydrogenated with ethylene oxide; and LABRAFIL 2125 is a polyoxyethylated almond oil. As described in the literature, MAISINE is a glyceryl monolinoleate; and IMWITOR 742 is caprylic/capric glyceride. The second formulation disclosed in Belgian Patent No. 895,724 comprises 15-20% [Dihydro-MeBmt]^1-[Vall]^2-Ciclosporin, 2-5% ethanol, 40-60% MAISINE and 10-40% IMWITOR 742. Thus, the first formulation disclosed by Belgian Patent 895,724 contains Labrafil and ethanol as co-solvents. The second formulation also contains ethanol.

The second formulation disclosed in Belgian Patent No. 895,724 comprises 15-20% [Dihydro-MeBmt]^1-[Val]^2-Ciclosporin, 2-5% ethanol, 40-60% MAISINE and 10-40% IMWITOR 742. This formulation also contains

Claim 1 is distinguished from the disclosure of Belgian Patent 895,724 since claim 1 presently recites recite "a pharmaceutical composition for oral administration comprising: a) a cyclosporin as active ingredient in a carrier medium consisting essentially of b) a fatty acid triglyceride and c) a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester. Claim 27 which depends from claim 1 and claims 32-37 which eventuate from claim 1 are therefore also distinguished from the teachings of Belgian Patent 895,724. Claims 2, 3, 5-7, and 10-14 are distinguished from Belgian Patent 895,724 since claim 2 recites "a pharmaceutical composition for oral administration comprising a cyclosporin as active ingredient in a carrier medium consisting essentially of b+ c) a transesterification product of a

hydrogenated vegetable oil with glycerol or propylene glycol." Claim 3 as presently amended recites "a composition according to claim 2 comprising b+c) a transesterification product of a hydrogenated vegetable oil and glycerol" and is therefore distinguished from the teachings of Belgian Patent '724. Claims 5-7 depend or eventuate from claim 3. Claims 4 and 8 are presently canceled. Claims 10-14 depend from claim 3. Claim 17 is canceled. Claims 18-24 eventuate from claim 3 as does claim 26. Withdrawal of the rejection of claims 1, 28-30 and 32-37 is therefore respectfully requested.

Claims 28 and 31 have also been rejected under 35 U.S.C.§ 103 as allegedly obvious over the Belgian Patent '724 in view of Applicants' admission of the prior art at page 9, lines 26-30; page 15, lines 17-32; and page 19, lines 16-18 and 21-22, of the specification. The Examiner states that it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimum proportions of Dihydrocyclosporin D and "CREMOPHOR®" RH 40" for use in the invention of the Belgian Patent '724 because the disclosure of the Belgian Patent '724 is not limited to any particular proportions of components in its pharmaceutical compositions and because it is routine in the art to determine all operable and optimal proportions of components in pharmaceutical compositions.

Applicants respectfully traverse the rejection of claims 28 and 31 as obvious over Belgian Patent '724 for the following reasons. Claim 28 depends from claim 27 and as presently amended recites: "composition according to claim 27 wherein components (b) and (c) consist or consist essentially of the individual components of a trans-esterification product of a hydrogenated vegetable oil with glycerol, said composition: i) being free or substantially free of ethanol; or ii) comprising Ciclosporin or $[Nva]^2$-Ciclosporin as component a) ; or iii) comprising components (a) and (e') in a ratio of 1:at least 1 p.p.w. Claim 31 depends from claim 27 and recites a specific ratio of

components (a) to (e') as 1:1 to 25 p.p.w. As discussed above, the oral formulations disclosed by Belgian Patent '724 both comprise ethanol. There is no suggestion or motivation in the Belgian patent for oral compositions free of ethanol. Moreover, there is no suggestion in Belgian Patent '724 for use of a transesterification product of a hydrogenated vegetable oil as presently recited in the claims. The Examiner readily admits that in Example 1 of the Belgian Patent '724, the ratio of Dihydrocyclosporin D t o CREMOPHOR RH 40 is not 1 : at least 1 p.p.w. Absent a suggestion in the Belgian '724 patent for a pharmaceutical composition for oral administration comprising a cyclosporin as active ingredient in a carrier medium consisting essentially of a transesterification product of a hydrogenated vegetable oil with glycerol, wherein the composition is free or substantially free of ethanol, or wherein the composition comprises Ciclosporin or $[Nva]^2$-Ciclosporin as component a) or wherein components (a) and (e') are in a ratio of 1:at least 1 p.p.w., or in the ratio of 1:1 to 25 p.p.w., the present invention is not obvious. Withdrawal of the rejection of claims 28 and 31 under 35 U.S.C.§ 103(a) is therefore respectfully requested.

The Examiner has rejected Claims 5 and 28 under 35 U.S.C.§ 103 as allegedly obvious over the Belgian Patent '724 in view of Applicants' admission of the prior art at page 9, lines 26-30; page 15, lines 17-32; and page 19, lines 16-18 and 21-22, of the specification as applied against claims 1-8, 10-14, 17-24, 26-30, and 32-37 above, and further in view of Cavanak (U.S. Patent No. 4,388,307. Applicants respectfully traverse the rejection of claims 5 and 28 under 35 U.S.C.§ 103(a) for the following reasons. Claim 5 depends from claim 3, which claim recites a transesterification product of a hydrogenated vegetable oil with glycerol or propylene glycol. Claim 28 depends from claim 27 and as presently amended recites: "composition according to claim 27 wherein components (b) and (c) consist or consist essentially of the individual components of a

trans-esterification product of a hydrogenated vegetable oil with glycerol, said composition:

i) being free or substantially free of ethanol; or ii) comprising Ciclosporin or $[Nva]^2$-Ciclosporin as component a) ; or iii) comprising components (a) and (e') in a ratio of 1:at least 1 p.p.w.

Applicants respectfully submit that there is no teaching or suggestion in Belgian Patent '724 for a pharmaceutical composition for oral administration comprising a cyclosporin as active ingredient in a carrier medium consisting essentially of a transesterification product of a hydrogenated vegetable oil with glycerol. Cavanak teaches oral dosage forms of cyclosporin comprising co-solvents, ethanol and vegetable oils such as olive oil and corn oil. Absent a suggestion in the combination of teachings provided by Belgian Patent '724 and Cavanak for the subject matter presently recited by claims 5 and 28, such claims are not obvious. Withdrawal of the rejection of claims 5 and 28 under 35 U.S.C.§ 103(a) is therefore warranted.

Claim 25 has been rejected under 35 U.S.C. §103 as allegedly obvious over the Belgian Patent '724 in view of Applicants' admission of the prior art at page 9, lines 26-30; page 15, lines 17-32; and page 19, lines 16-18 and 21-22, of the specification as applied against claims 1-8, 10-14, 17-24, 26-30, and 32-37 above, and further in view of Yamato et al. Yamato et al. (U.S. Patent No. 4,390,548) is cited form disclosing cacao butter as a standard inert diluent for solid unit dosage forms, including those coated with gelatin. According to the Examiner, it would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the cacao butter of Yamato et al as a diluent for the cyclosporin in gelatin capsule form of the Belgian Patent '724.

Applicants respectfully traverse the rejection of claim 25 under 35 U.S.C.§ 103(a) for the following reasons. The Belgian '724 patent does not teach or suggest a pharmaceutical composition for oral administration comprising a cyclosporin as active

ingredient in a carrier medium consisting essentially of a transesterification product of a hydrogenated vegetable oil with glycerol. Yamato et al. disclose a prostaglandin analogue. Yamato et al. do not teach or suggest a transesterification product of a hydrogenated vegetable oil and glycerol as presently recited by claim 25. In column 19, lines 22-24, Yamato et al. list diluents for use in solid compositions for oral administration of the subject prostaglandin analogue. Examples include calcium carbonate, potato starch, dextrin, alginic acid, lactose, mannitol, glucose or cacao butter. It is respectfully submitted that neither reference provides the suggestion or motivation to combine the teachings provided therein. Even if *pro arguendo*, there was a suggestion in either or both Belgian Patent '724 or Yamato et al., to combine the separate teachings provided therein, one skilled in the art would still not arrive at Applicants' invention. Absent a suggestion in the combination of Belgian Patent '724 and Yamato et al. for a pharmaceutical composition for oral administration comprising a cyclosporin as active ingredient in a carrier medium consisting essentially of a transesterification product of a hydrogenated vegetable oil and glycerol wherein the composition is admixed with a natural fat such as cacao butter, the subject matter of claim 25 is not obvious. Withdrawal of the rejection of claim 25 under 35 U.S.C. §103(a) is therefore warranted.

The Examiner has rejected Claim 1 under 35 U.S.C. §102(b) as allegedly anticipated by Chemical Abstract 92:64765k. Chemical Abstract 92:64765k has been cited for allegedly teaching a pharmaceutical composition comprising Cyclosporin A, an ester of a triglyceride with a polyalkylene glycol, e.g., "LABRAFIL M 1944", a fatty acid triglyceride, and a mono-or di-glyceride. Applicants respectfully traverse the rejection of claim 1 under 35 U.S.C. § 102(b). Claim 1 as presently amended recites "a pharmaceutical composition for oral administration comprising a cyclosporin as active ingredient in a carrier medium consisting essentially of b) a fatty acid triglyceride and c)

a glycerol fatty acid partial ester or propylene glycol or sorbitol complete or partial ester." Claim 1 is therefore distinguished from Chemical Abstract 92:64765k. Withdrawal of the rejection of claim 1 under 35 U.S.C.§ 102(b) is therefore respectfully requested.

The Examiner requested that applicants review claim 21 in order to determine whether "capric" might have been intended instead of "caproic". In response, Applicants have corrected the specification on page 18, line 5, to replace "capric" with "caproic".

Accordingly, in view of the amendments to the specification and claims, as well s the remarks hereinabove, the presently claimed invention is in condition for allowance, which action is earnestly solicited.

Respectfully submitted,

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